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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/084,471	05/22/1998	PATRICIA D. MURPHY	5371.31.US02	5585

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/084,471	MURPHY ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-94* is/are pending in the application.

4a) Of the above claim(s) *62-84, and 87-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61, 85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. This action is in response to the amendment filed July 16, 2002. The Sequence Listing filed November 27, 2002 has been entered. This action contains new grounds of rejection and is made non-final.

Election/Restrictions

2. Claims 62-84 and 87-94, as well as the subject matter of claim 61(b), are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response of October 22, 2001. In this response, Applicants elected the invention of claim 61(a), nucleic acids comprising a BRCA2 gene containing a thymidine at a position in exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2.

In the response filed July 16, 2002, Applicants state that "examination of claims 57-94" is requested. However, it is noted that claims 57-60 were cancelled in the response of September 18, 2000. Applicants further state that claims 62-86 include the T substitution at position 171 of SEQ ID NO: 2 and thereby should be examined together with the elected subject matter. However, as set forth in the restriction requirement, Applicants are required to elect a single nucleic acid molecule. Each of the nucleic acid molecules set forth in claims 62-84 and 87-94 are distinct structurally and functionally from the nucleic acid of claim 61(a). The presence of each of the additional nucleotide variations alters the structure and the function of the nucleic acid and renders the nucleic acids distinct from one another. A nucleic acid having a nucleotide substitution at position 171 of SEQ ID NO: 2 would be distinct from a nucleic acid that

also includes a C at position 1342 of SEQ ID NO: 4, as opposed to an A at position 1342 of SEQ ID NO: 4. Each individual allele is distinct from each haplotype, and each of the haplotypes is distinct from one another. The requirement to elect a single nucleic acid was clearly set forth in the previous restriction, such that claim 62 was restricted from claim 61(a) since it is drawn to a nucleic acid containing an additional variation at position 1093 of SEQ ID NO: 134. See, for example, "E" on page 2 of the Office Action / Restriction Requirement of Paper No. 20. Accordingly, the restriction requirement is maintained.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see for example page 2 of the specification). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61 and 85-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide basis for the subject matter of claim 61 of a BRCA2 gene containing a thymidine at a position in exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2. In the amendments filed July 16, 2002 and September 18, 2000, Applicants state that basis for the amendments can be found in Figures 1, 2 and 3 and at pages 5-6 and 26-27 of the specification. However, in Figures 1 and 2, there is an "A" at the nucleotide position that represents position 171 of SEQ ID NO: 2. The specification does not appear to teach a variant of SEQ ID NO: 2 containing a "T" at position 171. The specification teaches 10 mutations that constitute 5 distinct haplotypes of the BRCA2 gene. However, none of these mutations constitutes an A to a T substitution and the specification does not describe any of these mutations as being present in Exon 15. The specification at page 27 refers to 5 mutations in BRCA2, at positions 2024, 4553, 4815, 5841 and 5972. However, these mutations do not result in a change of an A nucleotide to a T nucleotide and the specification does not define these mutations as occurring at position 171 of SEQ ID NO: 2 or as occurring at the "corresponding" location in exon 15. Further, at page 26, the specification describes an alteration in exon 15. However, this alteration does not involve the nucleotide position 171 of SEQ ID NO: 2. The specification also discusses the detection of a mutation in exon 11. However, there is no specific discussion in the specification of a modification at position 171 of SEQ ID NO: 2 or of a nucleotide substitution of an A to a T in exon 15.

Accordingly, it does not appear that the specification as originally filed provides basis for the claim limitation of a BRCA2 nucleic acid comprising a nucleotide sequence variation wherein said variation is a thymidine at a position of exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2.

5. Claims 61, 85 and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to nucleic acids comprising a BRCA2 gene containing a nucleotide sequence variation wherein said variation is a thymidine at a position of exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2. The specification (see for example, pages 3-4) teaches that the BRCA2 nucleic acids can be used to diagnose susceptibility to cancer and to distinguish between individuals having a normal haplotypes and individuals having alleles or haplotypes associated with cancer (see for example page 5 of the specification). However, the specification does not teach an association between the presence of thymidine in exon 15 at a position corresponding to nucleotide 171 of SEQ ID NO: 2 and the occurrence of cancer. The specification uses a numbering system throughout that is based on the numbering system set forth in GenBank Accession No. U43746. The specification does not clarify how this numbering system relates to nucleotide position 171 of SEQ ID NO: 2. There does not appear to be any specific disclosure in the specification of a mutation at position 171 of SEQ ID NO:

2. In particular there is no disclosure of a specific mutation in exon 15 which results in the presence of a T at a position corresponding to position 171 of SEQ ID NO: 2, nor does the specification teach a specific association between such a mutation and cancer. The specification discusses 5 haplotypes that contain 10 nucleotide variations and which are referred to therein as BRCA2 $^{(omni1-5)}$. The specification at page 36 states that "A normal sample is one which is comparable to the BRCA2 $^{(omni1-5)}$ sequences and contains only minor variations which occur at minor polymorphic sites." However, the haplotypes do not appear to include a mutation at a position in exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2. There are no teachings in the specification as to the prevalence of the A to T mutation in normal individuals or in individuals having cancer. Additionally, there are no teachings in the specification as to how the claimed variation effects the amino acid sequence of BRCA2 and/or the functional activity of BRCA2 such that it would be apparent that this variation leads to an increased or decreased susceptibility to cancer. In the absence of any information on the specific mutation and its occurrence in the population or the functional activity of BRCA2 nucleic acids or proteins containing this mutation, further research would be required to determine how to make and use the claimed BRCA2 nucleic acids.

Additionally, the claims are broadly drawn to encompass nucleic acid molecules comprising a BRCA2 gene containing a nucleotide sequence variation of a thymidine at a position in exon 2 corresponding to nucleotide 171 of SEQ ID NO: 2. The claims include nucleic acids in which the sequences flanking the BRCA2 gene are not defined. Furthermore, the claims include nucleic acids which are defined only in terms of a single

nucleotide position. The claims do not require a particular sequence of BRCA2. It is clear that significant variation occurs in the BRCA2 sequence and that there are conflicting reports in the art as to what is considered to be the wildtype sequence for BRCA2. The specification states that several errors exist in the previously published GenBank sequence for BRCA2 and the specification teaches a "corrected" version of the BRCA2 gene. However, the claims do not clearly describe the BRCA2 gene sequences. Additionally, the claims are inclusive of all variants of BRCA2. However, as discussed in the specification, the sequences of the complete BRCA2 gene are important in determining whether the BRCA2 gene is normal or is associated with risk of developing cancer. The specification has not adequately taught the skilled artisan how to make and use a representative number of variants of BRCA2 which contain a T at a position in exon 15 and which contain any of the other possible mutations in the BRCA2 gene. There do not appear to be any teachings in the specification regarding variants having a T at a position in exon 15 corresponding to nucleotide 171 of SEQ ID NO: 2 and which contain any of the other recited variations in BRCA2 or any of the other known variations in BRCA2. Without knowledge of the relevance of the exon 15 mutation, it is unclear as to how the presence of flanking nucleotides of any identity and length will effect the resulting BRCA2 nucleic acid. The claims encompass nucleic acids which are defined only in terms of the fact that they contain a T at a position in exon 15. The specification and claims do not define the nucleotides of the BRCA2 gene flanking this T, nor the upstream or downstream nucleotides that flank the BRCA2 gene. The overall function of the nucleic acid comprising a BRCA2 gene containing the T in

exon 15 is also not defined. Accordingly, the specification has not provided sufficient guidance as to how to make and use a representative number of species within the claimed genus of nucleic acids comprising a BRCA2 gene that contains a T at a position in exon 15 corresponding to position 171 of SEQ ID NO: 2.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61, 85 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 61, 85 and 86 are indefinite over the recitation of "corresponding" because this is not an art recognized term and the specification does not provide a clear definition for this term. It is not clear if "corresponding" refers to the identical nucleotide position, a complementary nucleotide position or a nearby nucleotide position. Additionally, the claims do not clearly define the variation with respect to the overall BRCA2 gene. That is, defining the sequence variation with respect to a position in SEQ ID NO: 2 does not clearly define the variation with respect to the claimed nucleic acid comprising the BRCA2 gene. The claims should be amended to clarify the location of the variation with respect to exon 15 and the BRCA2 gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Carla Myers
April 5, 2004

CARLA J. MYERS
PRIMARY EXAMINER